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Aryldiazonium Salts Serve as a Dual Synthon: Construction of Fully Substituted Pyrazoles via Rongalite-Mediated Three-Component Radical Annulation Reaction

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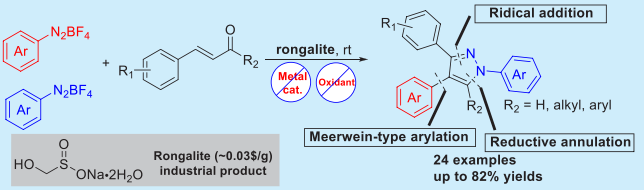
Supporting Information

ABSTRACT: A highly efficient rongalite-mediated three-component radical annulation reaction to furnish fully substituted pyrazoles from aryldiazonium salts and α,β-unsaturated aldehydes or ketones under metal- and oxidant-free conditions at room temperature has been developed. In this transformation, aryldiazonium salts served as the precursor of both the aryl and aryl hydrazine units. Mechanistic investigations indicated that rongalite could act as a radical initiator and reducing reagent simultaneously in the reaction.



Aryldiazonium salts are a class of inexpensive and readily available chemicals that have been used as versatile building blocks for a broad range of organic transformations.[1,2] According to the final form of the products, the reactions of aryldiazonium salts can be roughly divided into two subgroups: (i) Nitrogen-removal reactions and (ii) nitrogen-retention reactions. In the former subgroup, owing to aryldiazonium salts having a strong tendency to lose N_2, they have been used as aryl precursors in transformations such as C−C bond construction through Pschorr biaryltricycle synthesis[3] and Meerwein-type alkene functionalizations[4] (Scheme 1A(a)), C−X bond construction (X = halogen), through Balz−Schiemann-type reactions (F)[5] and Sandmeyer-type reactions (Cl, Br)[6] (Scheme 1A(b)), and to generate C−S,[7] C−P,[8] and C−B[9] bonds (Schemes 1A(c)−(e)). In the latter subgroup, aryldiazonium salts can act as highly active electrophiles in Japp−Klingemann-type reactions[10] and N−N bond formation reaction with amidine[10c] (Scheme 1A(f)), as radical receptors in radical addition reactions[11] (Scheme 1A(g)), and generate highly active intermediates *in situ* for subsequent cycloaddition reactions[12] (Scheme 1A(h)). However, examples combining both nitrogen-removal and nitrogen-retention reactions are rare. In 2015, Heinrich and co-workers reported a base-induced Meerwein-type carboamination reaction of alkenes with aryldiazonium salts, where aryldiazonium salts acted as both aryl precursors and radical receptors[13] (Scheme 1B). Recently, Wu[14] and Tu[15] reported novel reactions in which aryldiazonium salts acted as dual synthons. Despite these advances, the development of aryldiazonium salts for use as dual synthons in new multicomponent radical annulation reactions that allow efficient construction of useful heterocycles is still in demand. Herein, we report a novel rongalite-mediated three-component radical annulation reaction to construct fully substituted pyrazoles (Scheme 1C). Notably, rongalite acts simultaneously as a radical initiator and reducing agent in the reaction. To our knowledge, this is the first example of aryldiazonium salts serving as dual synthons to participate in radical annulation reactions to obtain fully substituted pyrazoles, acting as the precursor of both the aryl and aryl hydrazine units. This synthetic method provides a simple and straightforward approach to construct diverse pyrazole derivatives, which are privileged scaffolds present in synthetic[16] and natural products of medicinal interest,[17] such as Celebrex (a selective COX-2 inhibitor),[18a] Lonazolac and Difenamizole (nonsteroidal anti-inflammatory drugs),[18b] and Novalgin (an analgesic).[18c]

Initially, we explored the optimal conditions of this reaction using benzenediazonium tetrafluoroborate (**1a**) and benzylideneacetone (**2a**) as the model substrates (Table 1). Pleasingly, when we performed the reaction with rongalite in ethanol at room temperature, 5-methyl-1,3,4-triphenyl-1*H*-pyrazole (**3a**) could be obtained in 28% yield (entry 1). Encouraged by this promising experimental result, we then systematically screened the reaction conditions to obtain **3a** in higher yield. First, different solvents were examined, such as DCE, PhMe, $CHCl_3$, MeCN, DMSO, acetone, 1,4-dioxane, and THF, and the results showed that DMSO was screened as

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Scheme 1. Reactions of Aryldiazonium Salts

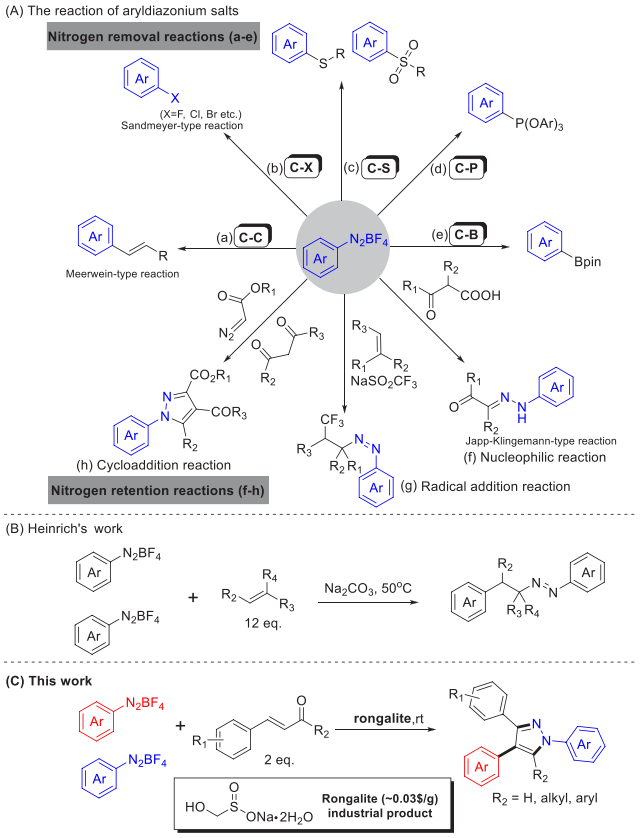
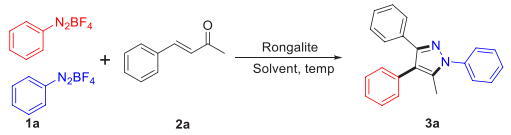


Table 1. Reaction Optimization[a]



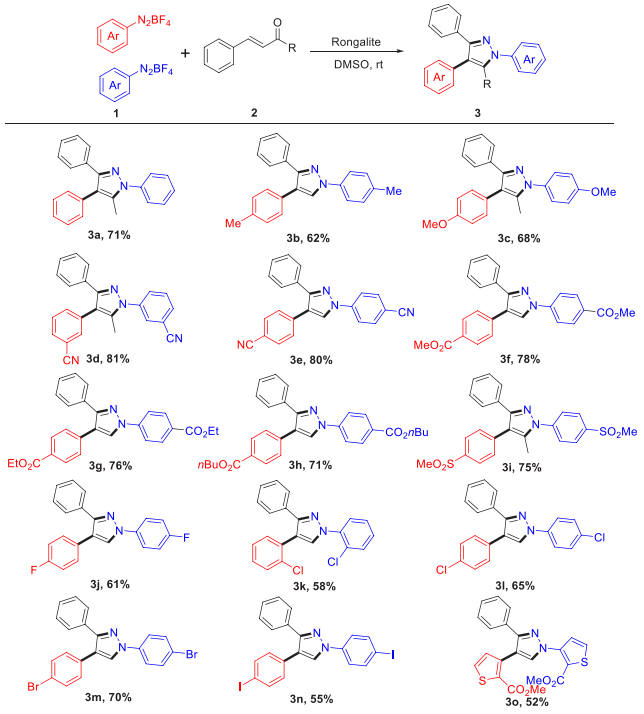
entry	solvent	1a:2a	temp (°C)	yield[b] (%)
1	EtOH	1.0:1.0	rt	28
2	DCE	1.0:1.0	rt	0
3	PhMe	1.0:1.0	rt	0
4	$CHCl_3$	1.0:1.0	rt	0
5	MeCN	1.0:1.0	rt	0
6	DMSO	1.0:1.0	rt	55
7	Acetone	1.0:1.0	rt	0
8	1,4-Dioxane	1.0:1.0	rt	0
9	THF	1.0:1.0	rt	0
10	DMSO	1.0:1.5	rt	63
11	**DMSO**	**1.0:2.0**	**rt**	**71**
12	DMSO	1.0:2.5	rt	60
13	DMSO	2.0:1.0	rt	51
14	DMSO	1.0:2.0	40	70
15	DMSO	1.0:2.0	50	68
16	DMSO	1.0:2.0	60	67
17[c]	DMSO	1.0:2.0	rt	68
18[d]	DMSO	1.0:2.0	rt	61

[a]Reaction conditions: **1a** (1.0 mmol), **2a** and rongalite (2.0 mmol) in solvent (3.0 mL) heated within 30 min. [b]Isolated yields based on **1a**. [c]Rongalite (1.5 mmol). [d]Rongalite (2.5 mmol).

the optimal reaction solvent (entries 2−9). Subsequently, the molar ratios of the two reactants **1a** and **2a** were also investigated; reaction with **1a**:**2a** (1:2) gave the best result (entries 10−13). Various temperatures were then screened, showing that room temperature was the best choice (entries 14−16). Finally, the dose of rongalite was evaluated (entries 17−18), with the results showing that 2.0 equiv of rongalite were optimal for this reaction.

Subsequently, we systematically evaluated the substrate scope of this radical annulation reaction in optimal reaction conditions (Scheme 2). Pleasingly, the results showed that the

Scheme 2. Substrates Scope of Aryldiazonium Salts and *α,β*-Unsaturated Ketones[a,b]



[a]Reaction conditions: **1** (1.0 mmol), **2** (2.0 mmol), and rongalite (2.0 mmol) in 3.0 mL DMSO at room temperature within 30 min. [b]Isolated yields based on **1**.

reaction was applicable for a variety of aryldiazonium tetrafluoroborates. Aryldiazonium tetrafluoroborates bearing an electron-neutral (4-H), electron-donating (4-Me, 4-OMe), and electron-withdrawing (3-CN, 4-CN, 4-CO_2Me, 4-CO_2Et, 4-CO_2*n*Bu, and 4-SO_2Me) substituent on their phenyl ring could all be successfully achieved, affording the corresponding polysubstituted pyrazoles in moderate to good yields (62−81%, **3a**−**3i**). The optimal conditions were also tolerated with halogenated (4-F, 2-Cl, 4-Cl, 4-Br, and 4-I) substrates (55−70%, **3j**−**3n**), which provide opportunities for further functionalization. Moreover, the optimal conditions were also applicable for heteroaryl aryldiazonium tetrafluoroborates, such as 3-carboxylate-2-thiophenyl, affording the corresponding polysubstituted pyrazoles in moderate yield (52%, **3o**). In addition, the exact structure of **3e** was further confirmed by single-crystal X-ray crystallography (see the Supporting Information (SI)).

Encouraged by these results, we next examined the scope of *α,β*-unsaturated aldehydes and ketones (**2**) (Scheme 3). Pleasingly, *α,β*-unsaturated aldehydes with electron-donating (4-Me, 2-OMe) and electron-withdrawing (4-F, 4-Cl)

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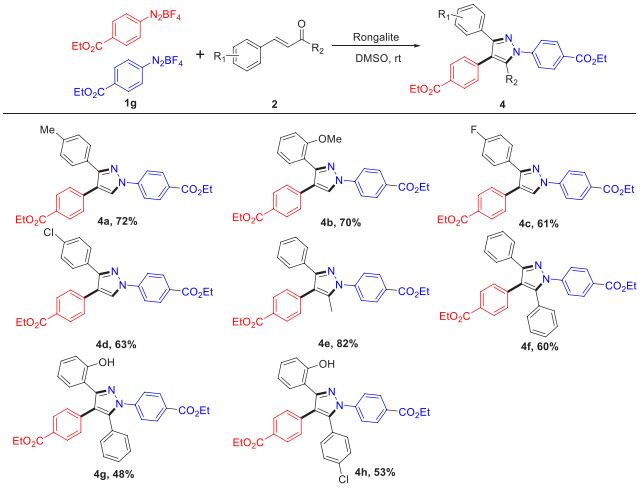
Scheme 3. Substrates Scope of α,β-Unsaturated Aldehydes and Ketones[ab]

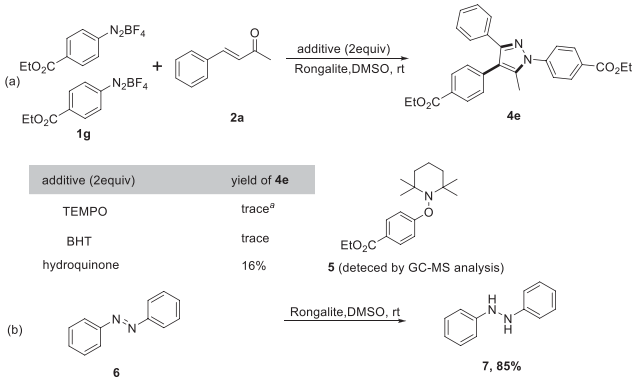


[a]Reaction conditions: **1g** (1.0 mmol), **2** (2.0 mmol), and rongalite (2.0 mmol) in 3.0 mL of DMSO at room temperature within 30 min. [b]Isolated yields based on **1g**.

substituents on their phenyl ring could all be successfully achieved, affording polysubstituted pyrazoles in moderate to good yields (61−72%, **4a**−**4d**). The optimal conditions were also applicable for α,β-unsaturated ketones, such as benzylideneacetone and chalcone, affording the polysubstituted pyrazoles in moderate to good yields (48−82%, **4e**−**4h**).

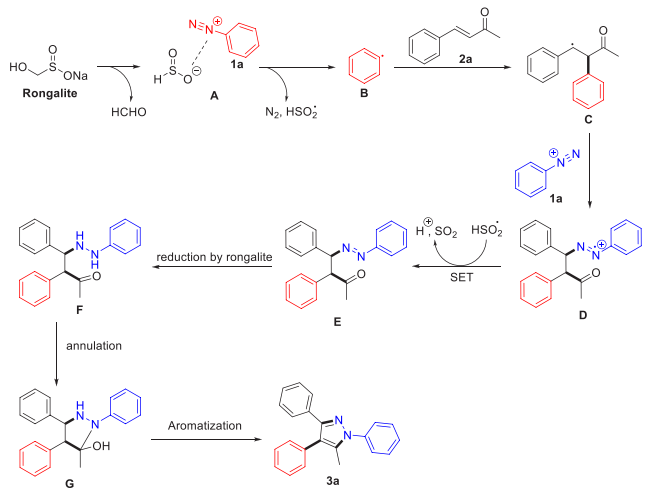
After the scope of this radical annulation reaction established, we then focus on evaluating the reaction mechanism (Scheme 4). When 4-(ethoxycarbonyl)benzenediazonium tetrafluoroborate (**1g**), benzylideneacetone (**2a**), and rongalite were treated with a radical capture reagent, such as, TEMPO, butylhydroxytoluene (BHT), or hydroquinone, the reaction was strongly inhibited, with no desired product (**4e**) obtained in the presence of TEMPO and BHT and only a 16% yield of **4e** obtained in the presence of hydroquinone (Scheme 4a). Especially, in the reaction of adding TEMPO, the TEMPO−$PhCO_2Et$ adduct **5** was detected by GC−MS analysis, indicating that this reaction may proceed through the radical process. To confirm the reduction ability of rongalite toward aryldiazo compounds, the reaction of (*E*)-1,2-diphenyldiazene (**6**) and rongalite in DMSO was performed, affording corresponding reduction product 1,2-diphenylhydrazine (**7**) in 85% yield (Scheme 4b). This indicated that aryldiazo compounds could be reduced to hydrazine by rongalite.

Scheme 4. Control Experiments



Based on our experimental observations and related literature reports,[19] we propose a possible mechanism for this radical reaction using benzenediazonium tetrafluoroborate (**1a**) and benzylideneacetone (**2a**) as an example in Scheme 5.

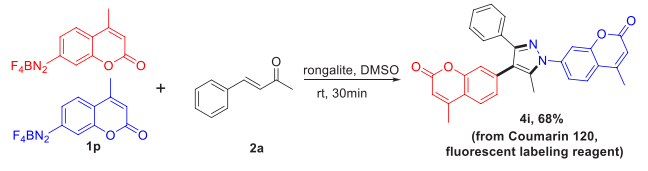
Scheme 5. Possible Mechanism



First, rongalite was decomposed to generate a HSO_2^- anion, with the release of formaldehyde. At the same time, aryldiazonium cation **1a** then combined with a HSO_2^- anion to form the complex **A** with the help of electrostatic interaction.[19c] The phenyl radical **B** and $HSO_2^\bullet$ radical were generated by a single-electron transfer reaction from complex **A**. Next, the Meerwein-type arylation of phenyl radical **B** and benzylideneacetone (**2a**) provides radical **C**, which can then be trapped by another molecule of **1a** to afford radical cation **D**. Subsequently, a single-electron transfer occurs at **D** with the $HSO_2^\bullet$ radical to generate diazo intermediate **E**,[19d] which is then reduced to corresponding hydrazine intermediate **F**. Finally, intermediate **F** undergoes sequential annulation and aromatization to generate the corresponding pyrazole product **3a**.

Moreover, we have also explored the applications of this three-component radical annulation reaction, as shown in Scheme 6. This method is very meaningful for incorporating a pyrazole ring into natural products which contained an aniline backbone. We conducted the late-stage modification with naturally occurring coumarin 120 and obtained the corresponding pyrazole **4i** in 68% yield.

Scheme 6. Late-Stage Modification



In conclusion, we demonstrate an efficient fully substituted pyrazoles synthesis from aryldiazonium tetrafluoroborates and α,β-unsaturated aldehydes or ketones under metal- and oxidant-free conditions at room temperature. Notably,

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rongalite acts simultaneously as the radical initiator and reducing agent in this reaction, while aryldiazonium tetrafluoroborates serve as dual synthons. This pyrazoles synthesis is green and practicable, with wide substance scope. Further studies to develop new multicomponent radical tandem reactions by using rongalite as a versatile reagent for other important heterocycles are being explored in our lab.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b03212.

Experimental procedures, product characterizations, crystallographic data, and copies of the ^{1}H and ^{13}C NMR spectra (PDF)

Accession Codes

CCDC 1888713 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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